DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Manufacturing and Product Quality, HFD-320
7520 Standish Place
Rockville, Maryland 20855-2737

TELEPHONE: (301) 594-0093
FAX: (301) 594-2202

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WARNING LETTER

JAN 8 1999

Mr. George Wilke
President
Novocol Pharmaceutical of Canada, Inc.
25 Wolseley Court
Cambridge, Ontario NIR 5S9
Canada

Dear Mr. Wilke:

The Food & Drug Administration has completed its review of the inspection of your sterile pharmaceutical product manufacturing facility in Cambridge, Canada, by Investigator Christine Marmara and Microbiologist Chryste D. Best during the period of October 19 - 23, 1998. The inspection revealed significant deviations from current good manufacturing practices (CGMP) in the manufacture of processed sterile drugs. The deviations were presented to your attention on an FDA-483 List of Observations at the close of the inspection. These CGMP deviations cause your sterile pharmaceuticals to be unacceptable for use in the United States, since, under United States law, the CGMP deviations render your products adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

PRODUCT NON-STERILITY

1. Your firm shipped numerous lots lacking evidence of sterility and conformance to sterility testing requirements.

Specifically, since April, 1997, at least batch sterility failures have occurred at your firm. of these batches have been released upon re-testing, with each of these failures attributed to "inadvertent contamination while performing the sterility test." *However, there was little or no data to support this repeated conclusion.*

Consequently, the decisions to disregard the sterility positive results and to perform re-testing were not justified.

The other batches were still under investigation at the time of the inspection.

When deviations occur during sterility testing, they should be documented concurrent with the test, investigated, and remedied. If any of these deviations may have compromised the integrity of the sterility test, the test should be invalidated immediately without incubation. Such deviations should be trended, with corrective measures taken in a timely manner. It is important to note that an unreliable laboratory is an objectionable condition and would serve only to further underscore the need to err on the side of safety rather than risk *overlooking a genuine production problem.*

Within your written response to this letter, include an updated and complete list of all initial sterility test failures for all sterile product batches produced since Jan. 1, 1996. (Include batch number, any associated sub-lots, and batch disposition.)

2. The investigations into these sterility test failures were inadequate in that:

a) Investigations failed to address the correlation between microorganisms found in the manufacturing environment and those found in units which tested positive.

We note that many microorganisms found in these sterility positive units were the same genus or species detected in the processing room during the manufacture of the concerned batch, or in the period preceding or following its production. processing room environmental monitoring results were beyond established limits during the processing of some of these batches.

was found times in the manufacturing environment during the period of May 14-16, 1998. Lot (Lidocaine and Epinephrine for Injection), which was contaminated with was filled on May 15 and 16 A result was also beyond the environmental monitoring limit during the manufacture of this lot. The investigation permitting release of this product lot to commercial distribution was signed and approved by the Director of

Moreover, the same microbiological species found in sterility positive units have been found as contaminants in the performed in 1997-1998 (e.g.,

b) Investigations failed to adequately address the role of production personnel in the failures. Crucial information such as personnel monitoring data and practices were absent from written investigation reports.

Because personnel are considered to be the source of most contamination in processing operations, practices, adequacy of training, and the microbial quality (microbiological count, identification) of gloves on the day of the are among the integral parts of any sterility test failure investigation.

We also note that the origin of sterility test positive contaminant in lot of Lidocaine and Epinephrine Injection was not adequately addressed.

c) Most investigations failed to provide any follow-up measures. In other instances, corrective actions were generally insufficient.

We note that most written investigation reports lacked the conclusion that retraining of any personnel (i.e., neither manufacturing nor testing) was necessary.

d) Many investigations appeared to clearly indicate the manufacturing operation was the origin of contamination. Nonetheless, lot release was primarily based upon sterility re-testing and a day procedure

Our inspection team also found that this procedure, which provides limited substance to a sterility test investigation, was done with a substitute for the actual test isolate on one occasion. (On another occasion, the test was not done at all, instead relying on past Finally, the stage sterility re-test samples were incubated for only days, *although your firm has found sterility test isolates later than day*

Because of the low sensitivity of sterility testing, a finding of no growth during retesting should be afforded minimal weight relative to other parts of the investigation. Further, when investigations into the origin of the product's contamination are inconclusive, the decision to release or reject the batch should err on the side of patient safety.

e) Investigations failed to address what sterility testing practices needed improvement until late September, 1998. Sterility failures

, were repeatedly attributed to the sterility testing analysts despite a lack of associated supporting data or evidence for this assumption, and little or no inquiry into the specifics regarding what practices might in fact be deficient.

To illustrate, the two possible sources which might lend some support to a conclusion of laboratory contamination either revealed no apparent problems or were absent. Specifically, no growth was observed in during the sterility test; and there was no personnel monitoring of the sterility testing analysts.

PERSONNEL MONITORING

3. The program for personnel monitoring of processing operators as well as sterility testing personnel was inadequate.

a) Monitoring of processing personnel was performed infrequently. Our inspection revealed that gloves of processing personnel are not sampled for long periods (e.g., multiple weeks between samples).

Personnel glove monitoring is performed daily on only randomly selected person. During a shift, at least people at a given time are normally permitted in a single processing room used to manufacture the products currently marketed to the US. Overall, approximately persons are permitted access to operations as part of the day, shift (hours each shift) sterile operation.

b) Personnel glove data was collected "for information only" and your firm's processing personnel glove quality standard is

No corrective measures were mandated by written SOPs if personnel monitoring results go beyond this limit. Our inspection found that, in these cases of high personnel glove fingerprint counts, follow-up measures such as assessing the impact on the concerned lot and operator retraining were not taken. We note that the relation of occurrences of high counts to sterility failures was not addressed. In addition, we find the glove (i.e., fingertip) standard of to be excessive for personnel performing processing operations. The goal for such personnel should be to regularly maintain contamination-free gloves.

c) There is no trending of personnel monitoring data.

d) Microorganisms isolated from personnel monitoring were not routinely identified.

e) Personnel who perform batch sterility testing are not monitored.

PERSONNEL CONTROL

4. Gowns worn by the operators performing processing operations lacked covering of forehead and cheeks.

Our inspection found that there have been a number of gowning qualification failures. We note that, after one failure, the evaluation report advised "try not to lean up against the machine too much." Please note that this practice is always unacceptable for an processing operator.

5. There is normally a personnel load of people in the main processing room in which simultaneous filling operations routinely take place.

ENVIRONMENTAL MONITORING

6. There was no trending of environmental monitoring data.

Trending of data is a fundamental aspect of monitoring the state of control of an processing operation. For example, data evaluation by line, location, person, shift, etc. should be assessed over the short and long term. We also note that when requested by the inspection team during the inspection, your firm provided a trending of out of limit data in the processing area, but this report contained omissions.

In your written response, please provide your program for monitoring critical contact surfaces (e.g., Such a program should target critical control points which directly contact the sterile product and container-closure components.

Your firm's response states that the ability of the drug formulation to inhibit growth of some microorganisms is the rationale behind not monitoring some surfaces (i.e., While your firm may use one of multiple acceptable approaches to develop a program for monitoring critical surfaces, the *rationale* provided in this case is not justifiable. In fact, your firm's formulations have been found to have substantial levels of bioburden (e.g., Mepivicaine lot

7. Active air samples were not taken at least during each shift for each

processing zone. Only of filling operations were sampled daily.

In your response, please clearly state whether active and settle plate air samples must be taken dynamically (during the course of a batch operation).

8. Sampling frequencies and locations were often not defined.

For instance, written procedures regarding surface and swab sampling did not include such fundamental aspects as sample locations and frequencies. Sampling was done times per week, and sampling technicians arbitrarily selected sample locations. Moreover, random testing was also done for system continuous sites.

9. Written procedures for environmental monitoring samples require only days of at These routine conditions are not adequate to sufficiently detect the spectrum of microorganisms that may be present in the processing area.

We note that your program also included fungi (yeast, mold) monitoring with conditions of days, and on specialized Data shows that molds have been detected several times in your manufacturing environments in 1998. Routine monitoring with the current day, conditions fails to provide adequate conditions to consistently recover fungi.

10. The program for monitoring nonviable particulates in areas is inadequate.

A sample was taken for only of filling operations. Additionally, the written procedure (SOP# permitted the nonviable sample to be taken under static conditions.

Your written response indicates that each filling area will be monitored per shift and does not mandate that these samples be taken under dynamic (operational) conditions. Please note that measurements to confirm air cleanliness at an processing line should be taken frequently during each shift at specified critical control points. Such monitoring should bracket the beginning and end of the operation.

QUALITY CONTROL UNIT (QCU)

11. The QCU failed to prevent the shipment of injectable product lots which appear to have a high likelihood of non-sterility. Rather than the Quality

Assurance Director, the Director of approved multiple investigation reports permitting release of batches which failed the sterility test. The Director of signed in lieu of, and in the space provided for, the QA Director.

Per the CGMP regulations, batch records, and associated investigations, are required to be reviewed and approved by the Quality Control Unit. Your firm should comprehensively review the adequacy of the quality control unit's overall role, function, and authority.

In addition, in your written response, please provide the written investigation and batch disposition for:

Lidocaine/Epinephrine batch
Injection

Lidocaine/Epinephrine batch
Injection

STERILITY TEST METHOD VALIDATION

12. Product sterility tests were not adequately validated. and were not included in product bacteriostasis and fungistasis validation as per the USP Monograph requirement.

PRODUCTION CONTROLS: TIME LIMITATIONS ON PRODUCTION

13. Time limitations on production had not been established for some significant process phases. For example, bulk product holding times were not established for multiple Lidocaine and Mepivacaine injectable products.

DESIGN

14. A single filling room contains multiple filling lines and is used for additional ancillary processing facility functions. As a result, there is unnecessary equipment and extra personnel load in the room in which injectable products are produced. At least filling machines are located and run simultaneously in the same room. In addition, this filling room is used for other functions such as storage. Environmental monitoring has shown this section of the room to be a persistent source of microbiological contamination over the last 18 months.

processing operations must be performed within separate, defined areas to prevent microbiological contamination, cross-contamination, or mix-ups (e.g., containers, closures, labeling). Each processing room should be

designed to minimize personnel load and activity adjacent to its filling line.

We also note multiple operational deviations occurred during 1998 (e.g., Please outline specific steps that your firm will take to prevent recurrence and confirm that written procedures have mandated the practice of running only one lot of a specific drug product in an processing room. In addition, respond with your firm's policy on line clearance.

MEDIA FILL (PROCESS SIMULATION) VALIDATION

15. Media fills do not adequately simulate the processing operation.

For example, media fills were not performed following the hour filling shifts which normally take place each of days a week. Instead, the room is "cleaned...and then prior to a media fill per SOP These SOP provisions represent best-case cleanroom conditions rather than simulating normal as well as worst-case operations.

As another example, normal operating conditions generally include: a high personnel load (as much as individuals) in the fill room, shift changes, opening and transferring sterile materials from the use of a etc. However, SOP only requires that of these aspects are simulated during a given media fill validation run. Both typical and atypical activities (e.g., interventions) should be simulated consistent with the number and consistency with which they occur during production. In addition, process simulations should be designed in a way that simulates operator fatigue from the lengthy operation.

Your firm's response does not state that issues regarding the length of the operation will be consistently addressed by a revised media fill program. It only appears to commit to simulating this aspect of your everyday operations in the *next* media fill.

16. Media fill acceptance criteria permit high contamination rates. Specifically, written procedures do not require an investigation of contamination unless the contamination rate "is greater than

The essential and central purpose of any process is to preclude any contamination. Shipment of any non-sterile unit in a lot is a prohibited act under the FD&C Act. Accordingly, any contaminated unit should be considered as objectionable and investigated as to its origin. Media failure investigations should include a comprehensive survey of all possible causes of the contamination including impact of the failure on commercial product produced on the line.

We acknowledge your correspondence, including the FDA 483 response and corrective action chart updates (Nov. 5 and 6, 1998; December 10 and 17, 1998). These responses fail to adequately discuss marketed lots, comprehensively address personnel practices and training of personnel, provide an adequate personnel or particulate monitoring program, include an adequate media fill program, provide adequate sterility testing and investigation procedures (SOP , or address many of the CGMP deficiencies in a global manner.

We recommend that you evaluate your facility on an overall basis for CGMP compliance. If you wish to ship your products to the United States, it is the responsibility of your firm to assure compliance with U.S. standards for current good manufacturing practices for pharmaceutical manufacturers.

The CGMP deviations identified above are not to be considered an all-inclusive list of the deficiencies at your facility. FDA inspections are audits which are not intended to determine all deviations from CGMPs that exist at a firm.

Until FDA has confirmed that your firm is in CGMP compliance, we will not recommend approval of any applications listing the facility as a supplier of sterile drug products. We have recommended your firm's products be placed on import alert and denied entry into the United States.

Please contact Compliance Officer Richard L. Friedman [telephone: (301) 594-0095; fax: (301) 827-0145] of this division at the above address if you have any questions. Please respond in writing to the above CGMP issues within thirty days. Within your response, detail corrective actions you plan to take or have taken to bring your operations into compliance. Include a timetable of when each of the corrections will be completed and attach supporting documents, as well as a complete list of FDA-regulated products shipped to the US. Please reference **CFN# 9615375** within your written response.

Upon receipt of this letter, we request immediate feedback on your firm's intentions regarding sterile products marketed to the United States. FDA is extremely concerned about the likelihood of non-sterility of batches of injectable product which are currently in U.S. distribution.

Finally, because of the urgency of this matter, we have sent a copy of this letter, on the date of its issuance, to your attention by facsimile.

To schedule a reinspection of your facility, after corrections have been completed and your firm has comprehensively evaluated overall compliance with CGMP requirements, send your request to: Director, International Drug Section,

HFC-134, Division of Emergency and Investigational Operations, 5600 Fishers Lane, Rockville, MD 20857. You can also contact that office by telephone at (301) 827-5655 or by fax at (301) 443-6919.

Sincerely,

Joseph C. Famulare

Joseph C. Famulare
Director
Division of Manufacturing & Product Quality